(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/075473 A1

(51) International Patent Classification[7]: C07D 453/02

(21) International Application Number:
PCT/IB2005/000221

(22) International Filing Date: 26 January 2005 (26.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/541,323 2 February 2004 (02.02.2004) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BASFORD, Patricia, Ann** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **POST, Ronald, James** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **SMITH, Julian, Duncan** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **TABER, Geraldine, Patricia** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **WOOD, David, J.** et al.; Pfizer Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

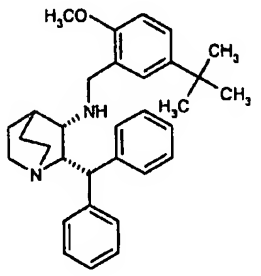
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

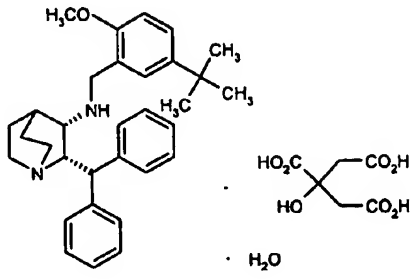
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARATION OF 1-(2S,3S)-2-BENZHYDR YL-N-(5-TERT-BUTYL-2-METHOXYBENZYL)QUINUCLIDIN-3-AMINE



(I)



(Ia)

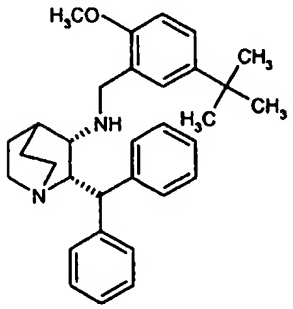
Ia – citrate monohydrate

(57) Abstract: This invention relates to an improved process for the preparation of (2S,3S)- 2-benzhydryl-N-(5-tent-butyl-2-methoxybenzyl)quinuclidin-3-amine, (hereinafter "compound of Formula I") and its pharmaceutically acceptable salts. In particular, the invention is directed to an improved synthesis of the monohydrate citrate salt of the compound of Formula (Ia).

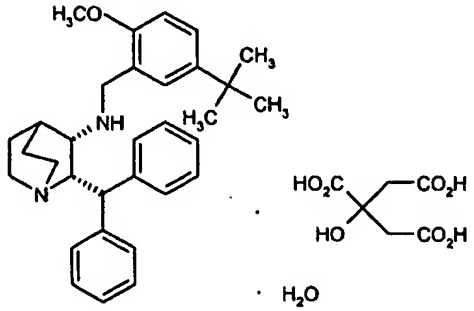
PROCESS FOR PREPARATION OF 1-(2*S*,3*S*)-2-Benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine

FIELD OF INVENTION

This invention relates to an improved process for the preparation of (2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine, (hereinafter "compound of Formula I") and its pharmaceutically acceptable salts. In particular, the invention is directed to an improved synthesis of the monohydrate citrate salt of the compound of Formula **Ia**.



I



Ia -- citrate monohydrate

BACKGROUND OF INVENTION

The compound of Formula **I**, an NK1 receptor antagonist, is effective as an anti-emetic agent for mammals. The compound of Formula I is the subject of U.S. 6,222,038 and U.S. 6,255,320, and the preparation of the compound of Formula I is described therein. U.S. 5,393,762 also describes pharmaceutical compositions and treatment of emesis using NK-1 receptor antagonists. The multiple-use formulation of the compound of Formula **I** may be parenterally administrated for about five days at the same site for treatment of emesis or other indications. Intravenous or, preferably, subcutaneous administration is desirable for acute use, since retention and absorption of an oral dosage form may be problematic during bouts of emesis. The multiple-use formulation is described in a co-pending U.S. provisional application No. 60/540897 assigned to and owned by Pfizer, Inc.

The compound of Formula I also improves anesthesia recovery in mammals. A co-pending U.S. provisional application No. 60/540,697 assigned to and owned by

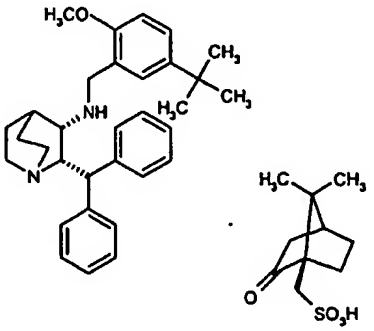
Pfizer Inc., describes a method of improving anesthesia recovery by administering a NK-1 antagonist prior to, during or after the administration of general anesthesia.

The text of the aforementioned applications and all other references cited in this specification are hereby incorporated by reference in their entirety.

Certain steps within the process description for synthesis of the monohydrate citrate salt of the compound of Formula I were conducted with reagents that are undesirable from a safety perspective and provided unsatisfactory yields for operation on a commercial scale. The present invention is directed to a process whereby the chemical conversions are carried out without the need for aggressive deprotection conditions, aggressive Schiff base-forming conditions or aggressive reducing agents, thus improving the intermediate and product quality and yield. The overall process is improved by use of common solvents for the key chemical conversion steps, by reduction in the number of intermediates requiring isolation, culminating in an overall yield improvement. Further efficiency was achieved by the ability to generate high enantiomeric - purity for the starting product (**VIa**), eliminating purification steps later in the process. Finally, the conditions used in the final step to manufacture the compound of Formula Ia have been optimized for the generation of the desired morphic form of the mono-citrate monohydrate salt of Compound of Formula I.

SUMMARY OF INVENTION

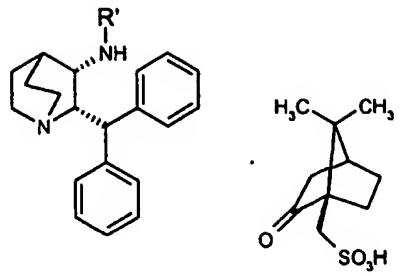
In one aspect, the invention is directed to a process for preparing the compound of Formula **Ib**,



Ib

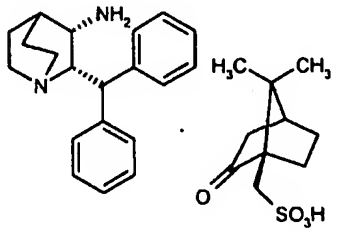
comprising:

(a) deprotecting a compound of Formula **VIa**,



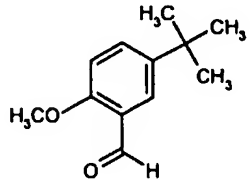
VIa

wherein R' is a protecting group, to provide a compound of Formula **VII**;



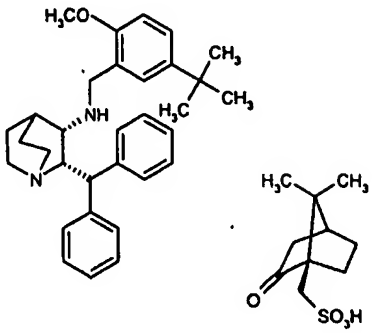
VII

(b) reacting the compound of formula **VII** so formed with a compound of formula **VIII**,



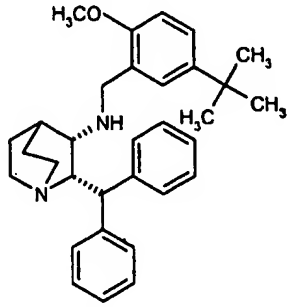
VIII

and performing a reductive amination to provide a compound of Formula **Ib**,



Ib

In one embodiment, the invention further comprises removing the camphorsulfonate salt of the compound of Formula **Ib** to provide a compound of Formula **I**,

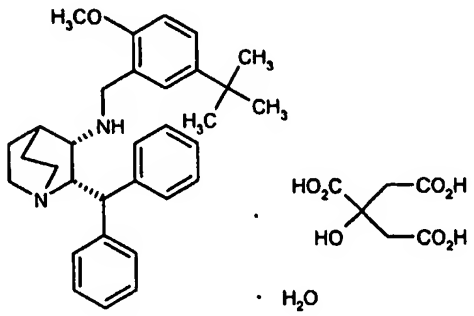


I

In a preferred embodiment, the protecting group is benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, or triphenylmethyl. Preferably, the deprotection is performed by catalytic hydrogenolysis with hydrogen. Preferably, the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

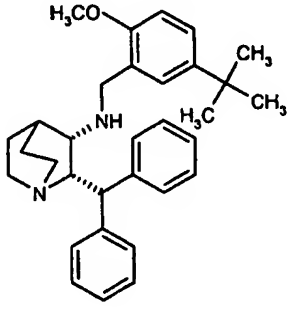
In a preferred embodiment, the reductive animation is performed by formation of an imine followed by catalytic hydrogenation. Preferably, the hydrogenation catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

In a preferred embodiment, the process further comprises treating the compound of Formula I with citric acid, forming the compound of Formula **Ia**.



Ia -- citrate monohydrate

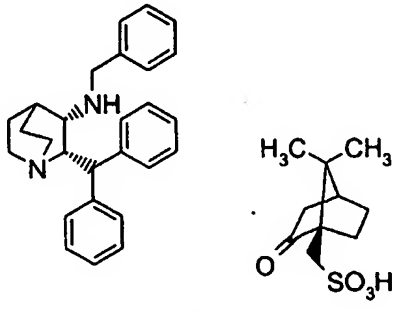
In a second aspect, the invention is directed to a process for preparing the compound of Formula **I**,



I

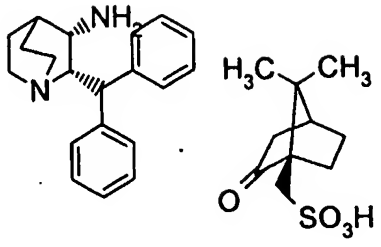
comprising:

(a) debenzylating a compound of Formula **VIa**



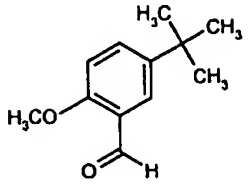
VIa

to provide a compound of Formula **VII**;



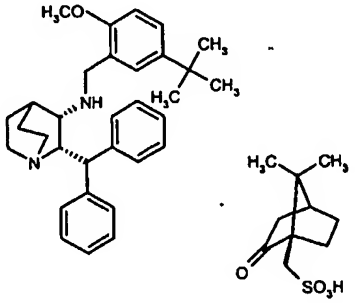
VII

(b) reacting the compound of formula **VII** so formed with a compound of formula **VIII**,



VIII

and performing a reductive amination to provide a compound of Formula **Ib**,



Ib , and

(c) removing the camphorsulfonate salt of the compound of **Ib** to provide the compound of Formula **I**.

In a preferred embodiment, the debenzylation is performed by catalytic hydrogenation. Preferably, the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

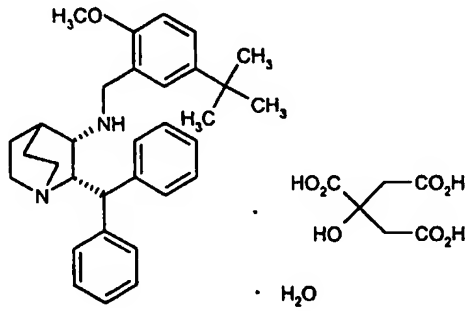
In a preferred embodiment, the process further comprises a reductive amination of step (b) that is performed by catalytic hydrogenation. Preferably, the

catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

In another embodiment, the process further comprises isolating the compound of Formula I. Preferably, the isolation of the compound of Formula I occurs by acid counter ion exchange or basification followed by selective crystallization. Preferably, the crystallization is accomplished in a solvent selected from water, alcohols, ethers, hydrocarbons or mixtures thereof. Preferably, the solvent is isopropanol, toluene or water or mixtures thereof.

In a preferred embodiment, the basification is performed by the addition of an inorganic or organic reagent. Preferably, the reagent is sodium hydroxide, sodium carbonate or sodium bicarbonate.

In another embodiment, the process further comprises treating the compound of Formula I with citric acid, forming the compound of Formula Ia



Ia -- citrate monohydrate

In a preferred embodiment, the process further comprises the addition of acetone and water. Preferably, the process further comprises

a) filtering the solution; and

b) adding a filtered ether solvent,

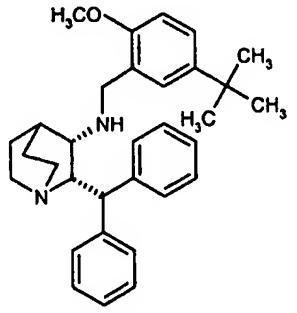
providing a compound of Formula Ia.

In another embodiment, the process further comprising the additional step (c) of granulating the compound of Formula Ia. Preferably, the ether solvent is tert-butyl methyl ether. Preferably, the process further comprises applying heat at an elevated temperature during step (b). Preferably, the process further comprises the addition of

seed crystals of Compound of Formula **Ia** during or after step (b). Preferably, the temperature is about 30°C to about 45°C.

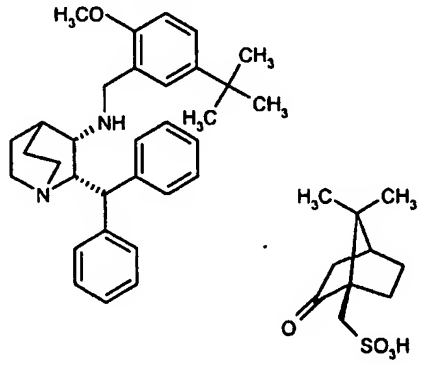
In another embodiment, the process further comprises granulating the compound of Formula **I** at an elevated temperature. Perferably, the temperature is about 30°C to about 45°C.

In a third aspect, the invention is directed to a process for preparing the compound of Formula **I**,



I

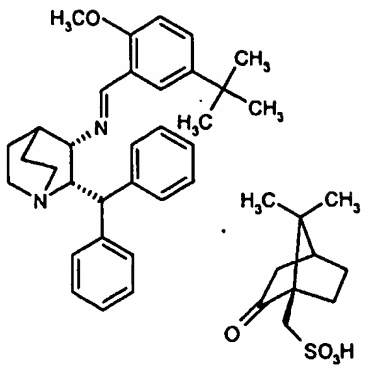
comprising removing the camphorsulfonate salt of a compound of **Ib**,



Ib

to provide the compound of Formula **I**.

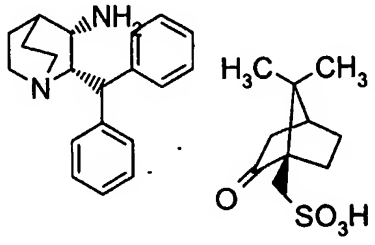
In a preferred embodiment, the process further comprises reducing a compound of **IXa,**



IXa

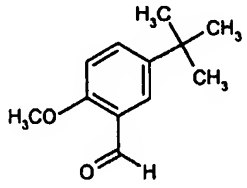
to provide the compound of Formula **Ib** so formed.

In a preferred embodiment, the process further comprises reacting a compound of Formula **VII,**



VII

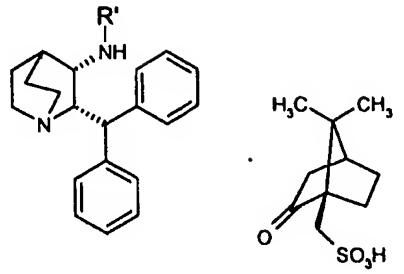
with a compound of Formula **VIII,**



VIII

to provide the compound of formula **IXa** so formed.

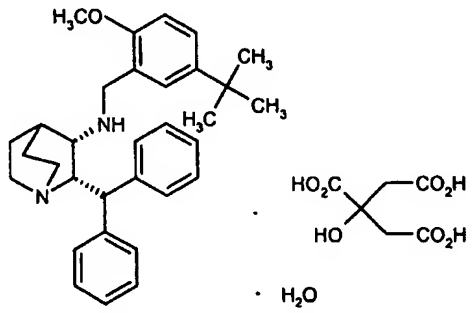
In a preferred embodiment, the process further comprises deprotecting a compound of Formula **VIa,**



VIa

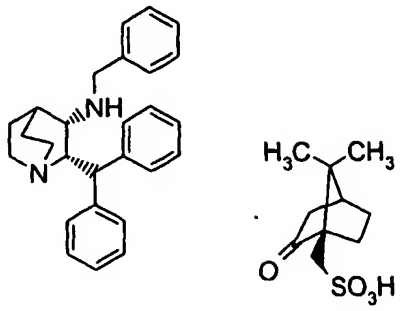
wherein R' is a protecting group selected from benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl or triphenylmethyl, to provide the compound of Formula **VII** so formed.

In a preferred embodiment, the process further comprises treating the compound of Formula I with citric acid to form a compound of Formula **Ia,**



Ia – citrate monohydrate

In a fourth aspect, the invention is directed to a compound of the Formula VIa,



VIa

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Compound of Formula Ia PXRD Pattern

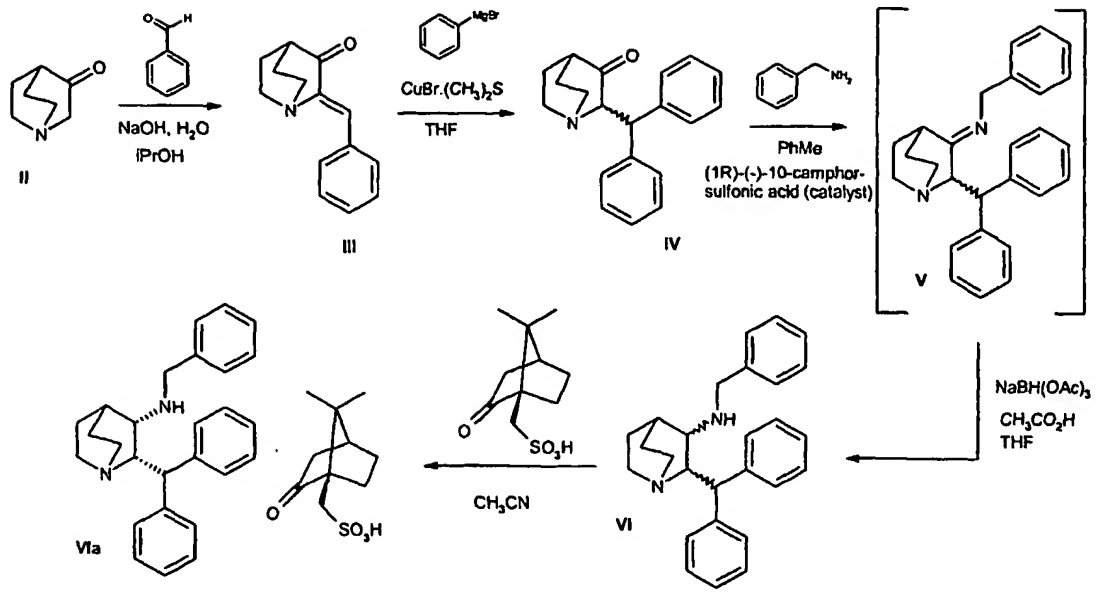
DESCRIPTION OF INVENTION

In general, the compound of Formula I may be prepared by methods that include processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compound of Formula I of this invention are illustrated by the following reaction schemes. Other processes are described in the experimental section. Some of the starting compounds for the reactions described in the schemes and examples are prepared as illustrated in Preparation A and Preparation B. All other starting compounds may be obtained from general commercial sources, such as Sigma-Aldrich Corporation, St. Louis, MO, or may be prepared using methods known in the chemical literature.

The following reaction Schemes illustrate one possible preparation of the compound of the present invention. One skilled in the art would recognize that other protecting groups, other than benzyl, could also be utilized to prepare protecting group variations of the compound of Formula **VIa**. For example, other possible protecting groups are 4-methoxybenzyl, 2,4-dimethoxybenzyl, and triphenylmethyl.

Preparation A and Preparation B schemes depict alternative preparations of the starting compound, compound of Formula **VIa**, later used in Schemes I and II, wherein benzyl is utilized as the protecting group.

PREPARATION A



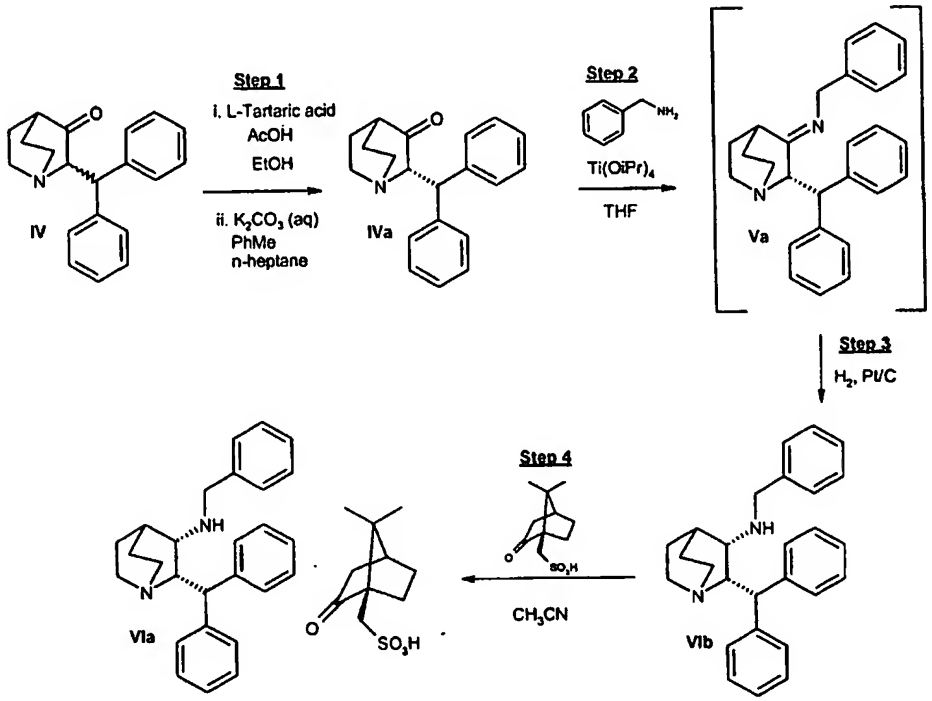
One possible synthesis of the compound of Formula **VIa** is detailed above in Preparation A. This route achieved optical purity of compound of Formula **VIa** by selective crystallization of the desired compound (cis 2S,3S form) as the (1*R*)-(-)10-camphorsulfonic acid salt from a racemic mixture of Compound VI. Up to 15% of the undesired *cis* enantiomer (cis 2R,3R form, typically 5-6%) and up to 2% of undesired trans diasteriomers (trans 2R, 3S and trans 2S, 3R forms, typically 1.3% observed), however, were produced in the process of synthesizing the compound of Formula **VIa** via this route.

With this particular approach to compound of Formula **VIa**, however, it is necessary to enhance and improve both optical and diastereomeric purity to achieve the desired quantity of compound of Formula **I**, prior to subjecting it to the synthetic route depicted in Scheme I.

An alternate synthesis to compound of Formula **V** and ultimately compound of Formula **VIa** is depicted in Preparation B. Preparation B is the subject of U.S. Non-provisional Application No. 10/679961, filed October 6, 2003. The text of the aforementioned application is hereby incorporated by reference in its entirety. As described above, one of ordinary skill in the art would recognize that different

protecting groups, other than benzyl, could be utilized to prepare variations of the compound of Formula **VIa**. These variations are within the scope of the present invention.

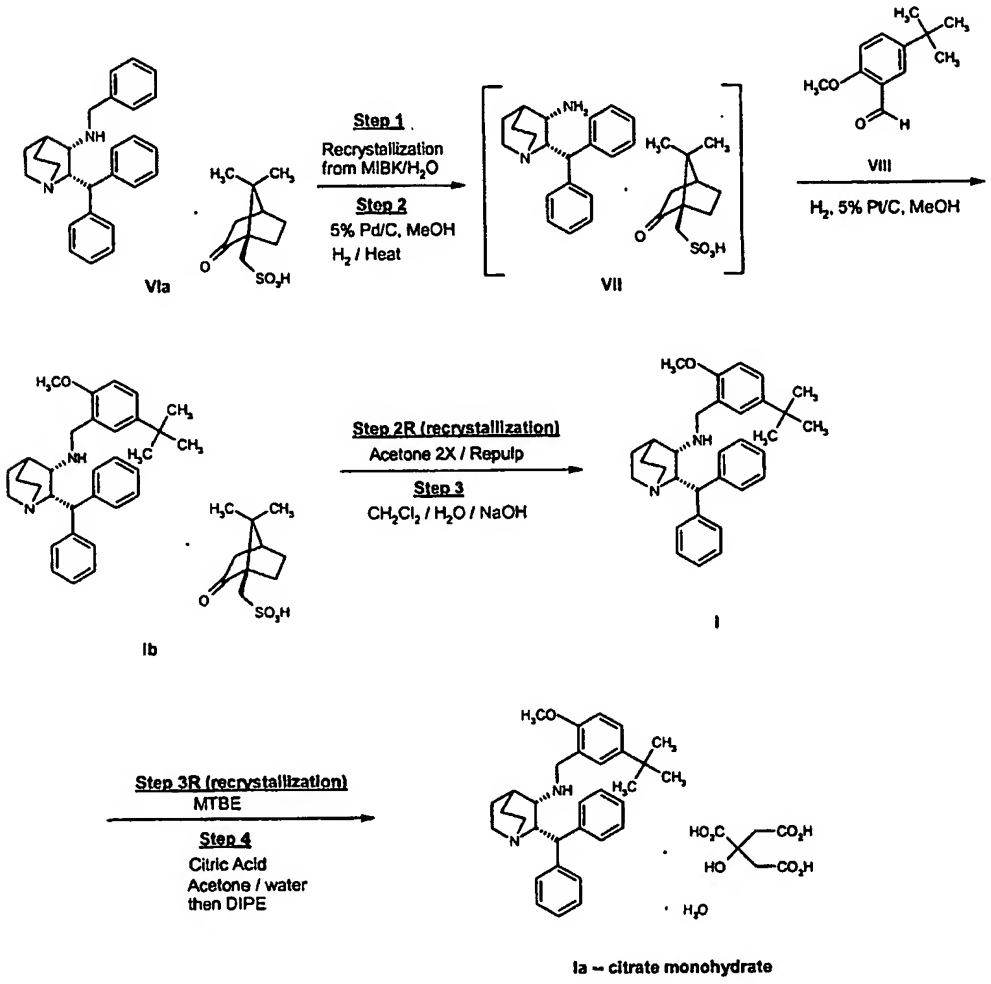
PREPARATION B



In Step 1 of Preparation B, the optical purification is first performed on the racemic ketone of Formula **IV**, the latter being dynamically resolved as the L-tartaric acid salt wherein the undesired (2*R*)-enantiomer is racemized under the reaction conditions to ultimately give the desired (2*S*)-enantiomer in greater than 50% yield. Optically pure compound of Formula **IVa** (up to 98% ee) was then reacted with benzyl amine under Schiff base-forming conditions to provide the imine intermediate, compound of Formula **Va**, which was catalytically reduced in a stereoselective manner to cis compound of Formula **VIb**. The compound of Formula **VIa** is produced in a higher optical (enantiomeric) purity when compound **VIb** it is converted to the (1*R*)-(-)-camphorsulfonate salt, eliminating the need for recrystallization of compound **VIa** to enhance stereochemical purity, when synthesized via the route described in Preparation B

The following reaction Scheme I illustrates an example of the preparation of the compound of Formula Ia from the compound of Formula **VIa**, as prepared via Preparation A.

SCHEME I



The compound of Formula **VIa** required additional purification to mimimize the presence of the undesired (cis 2R-3R)-enantiomer for use in the manufacture of compound of Formula I. Accordingly, in Step 1 of Scheme I, two successive recrystallizations of compound of Formula **VIa** were performed in 4-methyl-2-pentanone ("MIBK").

Compound **VIa** (50 g) was suspended in 10 volumes (500 mL) of 10% v/v water/MIBK solution) and heated to about 88-90°C for up to about 2 hours. The

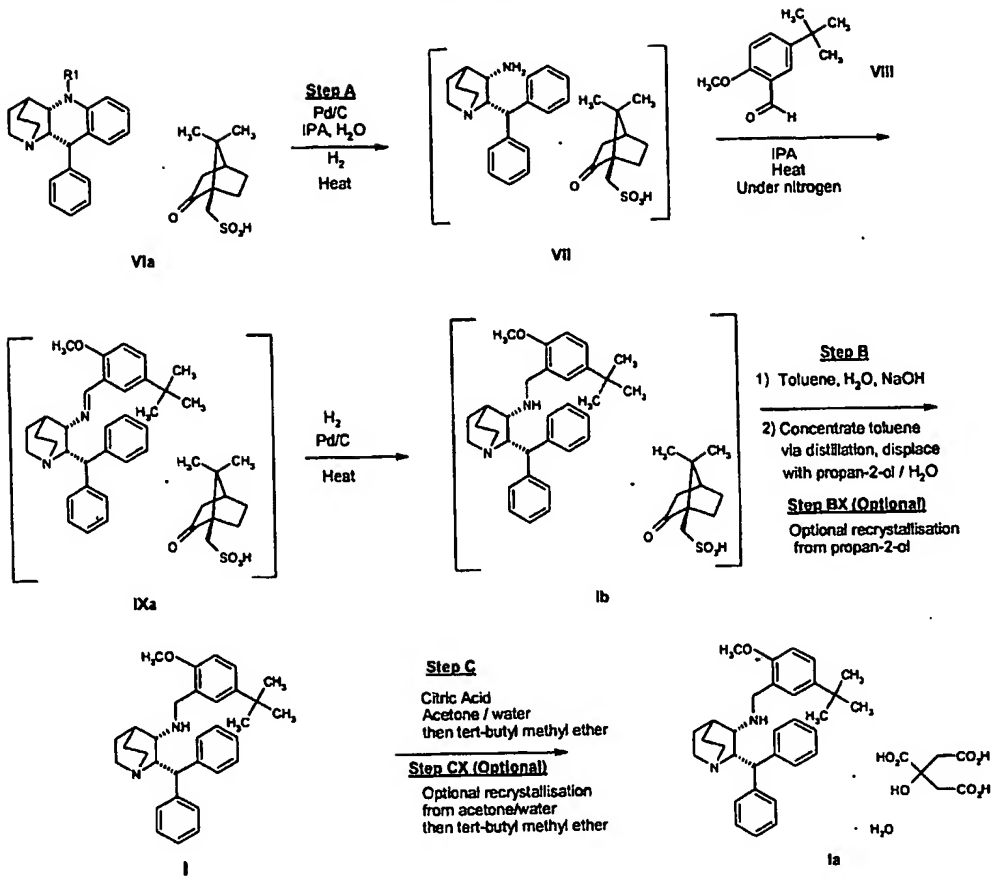
solution was cooled and the product isolated by filtration. The solvent wet product was re-suspended in 10 volumes of aqueous MIBK and heated again to about 88-90°C for up to two hours. The solution was then cooled to about 20-25°C and the product was isolated by filtration, washed with 0.5 volumes of MIBK and was then dried to yield Compound **VIa** in high enentiomeric purity (less than 0.2% of undesired enantiomer) in typically 83-85% yield.

In Step 2 of Scheme I, the compound of Formula **VIa** was catalytically deprotected, in this case, debenzylated, with a suitable catalyst, such as, palladium on carbon, palladium hydroxide on carbon, platinum on carbon, palladium on calcium carbonate , or palladium on alumina (Al_2O_3) , in a solvent, such as methanol or isopropanol (propan-2-ol, "IPA") to provide compound of Formula **VII** in situ. In this particular synthesis, it was not necessary to isolate the intermediate compound **VII**. Instead, compound **VII** was reacted with compound **VIII** and hydrogen in the presence of a suitable catalyst, such as palladium on carbon, palladium hydroxide on carbon, platinum on carbon, palladium on calcium carbonate , or palladium on alumina (Al_2O_3), to provide compound **Ib**.

Compound **Ib** was recrystallized using acetone as solvent to provide purified compound **Ib**. Compound I was then prepared from compound **Ib** by basification using aqueous sodium hydroxide and extraction into dichloromethane followed by recrystallisation from tertiary-butyl methyl ether. Compound I was then suspended in a mixture of acetone and water, and citric acid was added followed by diisopropyl ether. The resultant solid was then collected by filtration, washed with diisopropyl ether and then dried to give compound **Ia**.

The following reaction Scheme II illustrates an alternative preparation of the compound of Formula I citrate monohydrate from the compound of Formula **VIa**, with improved yield from about 68% to about 76% Furthermore, the reaction of Scheme II is improved in that intermediary compounds (bracketed) do not require isolation, before proceeding forward to the next synthetic step.

SCHEME II



In Step A of Scheme II, a mixture of compound of Formula **VIa**, wherein R^1 is a protecting group such as benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, or triphenylmethyl, in an alcoholic solvent such as methanol, ethanol or n-propanol but preferably propan-2-ol, optionally also in the presence of water, was hydrogenated over a palladium on carbon catalyst at elevated temperature (typically 75-80° C) and pressure (typically 50 psig hydrogen). One skilled in the art would appreciate that other catalysts may be suitable, such as palladium on carbon, palladium hydroxide on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

Once formation of the intermediate, compound **VII**, was complete (about 1 hour) the compound of Formula **VIII**, typically as a solution in the respective alcoholic solvent, such as methanol, ethanol etc. (preferably in propan-2-ol (isopropanol, "IPA")) was added to the reaction, without isolating the compound of Formula **VII**, and

the mixture stirred optionally at elevated temperature, from about 30°C to about 120°C, under an atmosphere of nitrogen. Once sufficient intermediate compound **IXa** was formed, the nitrogen atmosphere was replaced with hydrogen. The reaction was then stirred optionally at elevated temperature (about 30-120°C) and at elevated pressure (typically 50 psig) until the formation of the compound **Ib** was complete (typically 18 hours). The reaction mixture was then cooled (about 20-25°C) and the hydrogen gas vented. The palladium on carbon catalyst was removed by filtration, and the resultant solution of compound **Ib** was taken directly into Step B.

In Step B of the reaction scheme II, the solution of compound **Ib**, typically in a mixture of propan-2-ol and water, was concentrated by distillation followed by the addition of toluene. The mixture was then concentrated again by distillation, adding additional toluene and water as necessary during distillation until sufficient isopropanol had been removed from the mixture and an appropriate solution volume obtained (typically, 2-4 volumes per kg of compound **Ib**). Water and toluene were added as necessary (typically about 3.5 volumes of water and about 5 volumes of toluene). One skilled in the art would appreciate that other solvents, other than toluene, such as methylene chloride, ethyl acetate, isopropyl acetate or tert-butyl methyl ether, could be utilized. The pH was adjusted to an appropriate point (about 11.5 to 13.5) by the addition of aqueous sodium hydroxide and if necessary aqueous hydrochloric acid with stirring.

Once an appropriate pH has been obtained, the aqueous phase is removed by separation. The product-containing organic phase was then concentrated by distillation. A mixture of propan-2-ol and water was added and the mixture concentrated again by distillation. The addition of water and propan-2-ol and subsequent concentration by distillation was repeated as necessary until sufficient toluene (typically less than 3% w/w toluene by GC analysis) has been removed from the mixture and an appropriate solution volume has been obtained (about 4 volumes with respect to compound **Ib**), resulting in a composition of the solvent in the final granulation slurry of typically greater than 80% w/w propan-2-ol, less than 20% w/w water and less than 3%w/w toluene.

Once sufficient toluene has been removed, the mixture was cooled until crystallization occurs (typically 70-75°C). The resultant suspension was cooled further (typically to 20-25°C) and granulated for a period of time before being optionally cooled further to about 0-5°C and stirred for a period of time. The solid was collected

by filtration, and the filter cake washed with propan-2-ol and dried under vacuum at elevated temperature (typically 45-55°C) to provide compound of formula **I**, as a crystalline solid. One skilled in the art would appreciate that other solvents, other than propan-2-ol, such as methanol, ethanol, n-propanol, acetonitrile, isopropyl acetate, tertiary-amyl alcohol and 4-methyl-2-pentanone could be utilized.

As outlined in the optional Step BX of the reaction scheme, which is not typically required, compound **I** may be further purified. Compound **I** was suspended in propan-2-ol and the mixture heated at reflux to give a solution. The mixture was then heated at an elevated temperature below the reflux temperature (about 70-75°C) for about 1 hour during which time crystallization typically occurs. The resultant suspension was maintained at this temperature for a period of about 1 to 2 hours and then cooled (to about 20-25°C). After stirring at ambient temperature for a period of time (typically 1-18 hours), the solid was collected by filtration. The filter cake was washed with propan-2-ol and then dried under vacuum at elevated temperature (about 45-55°C) to provide a purified compound **I**, as a crystalline solid. One skilled in the art would appreciate that other solvents, other than propan-2-ol, such as methanol, ethanol, n-propanol, acetonitrile, isopropyl acetate, tertiary-amyl alcohol and 4-methyl-2-pentanone could be utilized.

In Step C of the reaction scheme, compound **I** (1 molar equivalent) andanhydrous citric acid (typically 1.1 molar equivalents) were combined in mixture of acetone (typically about 8-10 volumes) and water (typically about 0.4 volumes), and the resultant solution filtered. More acetone (typically about 2 volumes) was then added to wash the transfer equipment through. To the filtrate was added a filtered ether solvent such as methyl tertiary-butyl ether (tert-butyl methyl ether, "MTBE") or isopropyl ether ("IPE") (typically about 10 volumes), optionally at elevated temperature (30-45°C). Once crystallization occured, which may optionally be initiated by the addition of some seed crystals, the mixture was granulated for a period of time (typically 18 hours), typically at 20-25°C but optionally at elevated temperature (30-45°C) for a portion of this time. The solid is then collected by filtration. The filter cake was washed with the respective filtered ether solvent and then dried at a temperature less than 60°C (room temperature, if using isopropyl ether) under vacuum optionally with no air or nitrogen bleed to provide compound **Ia**, the citrate monohydrate, as a crystalline solid. The product may then be optionally milled or sieved.

In optional Step CX, the purity of compound **Ia** may be improved by dissolving **Ia** in a mixture of acetone (typically 7 volumes) and water (typically 0.3 volumes) at elevated temperature (about 35-50°C). The mixture was then cooled (to about 20-35°C) and optionally filtered. To the resulting mixture was then added a filtered ether solvent, such as tert-butyl methyl ether or isopropyl ether, optionally at elevated temperature (about 30-40°C). Once crystallization occured, which may optionally be initiated by the additions of some seed crystals, the mixture was granulated for a period of time (typically 18 hours), typically at 20-25°C but optionally at elevated temperature (30-45°C) for a portion of this time. The solid was then collected by filtration. The filter cake was washed with the respective filtered ether solvent and then dried at a temperature less than 60°C (room temperature, if using isopropyl ether) under vacuum optionally with no air or nitrogen bleed to provide compound **Ia**, the citrate monohydrate, as a crystalline solid. The product may then be optionally milled or sieved.

Other pharmaceutically acceptable salts, other than the citrate, may be utilized. For example, malate, maleate, mesylate, lactate, and hydrochloride salts or their *in situ* equivalents may be prepared by adding equimolar amount of the appropriate acid to the compound **I**, free base solutions.

GENERAL EXPERIMENTAL PROCEDURES

Recrystallization of compound of Formula VIa (Scheme I).

To a 3-L round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, thermometer and thermostated oil bath, was added compound **VIa** (200 grams), methyl-isobutylkentone ("MIBK") (1900 mL) and 100 mL of water. The suspension was gradually heated to reflux under stirring, about 30 minutes, and kept at 88-90°C for about 15-30 minutes, until achieving a complete solution. (The MIBK/water azeotrope boils at about 88 °C.) At this stage, the mixture was biphasic with a small amount of water undissolved.

The mixture was slowly cooled, while stirring, to room temperature (about 20-25 °C) in about 2 hours. The product began to precipitate at about 60 °C. The suspension was granulated at 20-25°C for about 2-3 hours, but also could be held overnight at 20°C, and the precipitate was filtered and washed with about 100 mL of MIBK.

The wet cake (about 220-230 grams) was recrystallized, as described above, using 1700 mL of MIBK and 91 mL of water. The suspension was again granulated for at least 3 hours or overnight at 20-25 °C. The product is filtered and washed with MIBK (100 mL). The purified compound **VIa** was dried in an air tray-drier at 50°C, until constant weight was obtained (about 18 hours), providing a white crystalline purified solid, compound **VIa**. Yield 85%. Chiral purity: (2R-*cis*) enantiomer 0.3-0.5%.

Preparation of (2*S*,3*S*)-2-Benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl) quinuclidin-3-amine (1*R*)-10-camphorsulfonate, compound of formula Ib, as a solution in propan-2-ol/water, (Step A, Scheme II).

To a mixture of (2*S*,3*S*)-2-benzhydryl-*N*-benzylquinuclidin-3-amine (1*R*)-10-camphorsulfonate (compound of formula VIa, 18.0 kg, 29.3 moles) and water (18.0 kg) in propan-2-ol (57.9 kg) was added 5% palladium on carbon, 50% water wet (2.88kg) and the resultant mixture was hydrogenated at 50psi hydrogen pressure at 75-80°C for 4 hours. The mixture was then cooled to 15-20°C, and the hydrogen atmosphere was replaced by nitrogen (5psi). To this mixture was then added a solution of 5-*tert*-butyl-2-methoxybenzaldehyde (6.47 kg, 33.7 moles) in propan-2-ol (6.47 kg). The addition line was then washed with propan-2-ol (4.24kg) and this was added to the reaction mixture, which was then stirred at 75-80°C for 2 hours under a nitrogen atmosphere. The resultant mixture was then cooled to 30-40°C, and the nitrogen atmosphere was replaced by hydrogen (50psi). The mixture was then hydrogenated at 50psi hydrogen pressure at 75-80°C for 3.5 hours, after which time the reaction was cooled to 25-30°C and the hydrogen pressure was reduced to 10psi for 10 hours for convenience. The reaction was then re-pressurised with hydrogen (50psi) and heated to 75-80°C for 11.5 hours, after which time the reaction was again cooled to 25-30°C and the hydrogen pressure was reduced to 10psi for 10 hours for convenience. The reaction was then re-pressurised with hydrogen (50psi) and heated to 75-80°C for 3 hours so that the total reaction time at 75-80°C was 18 hours. The reaction was then cooled to 15-20°C and the hydrogen atmosphere was replaced by nitrogen. The resultant suspension was then filtered to remove the catalyst, and the filter cake was washed with propan-2-ol (19.8 kg). The combined filtrate and washings, comprising a solution of (2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-

methoxybenzyl)quinuclidin-3-amine (1*R*)-10-camphorsulfonate (compound of formula Ib) in propan-2-ol/water, were taken as such into the next step, denoted as Step B.

Preparation of (2S,3S)-2-Benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine, compound of formula I (Step B, Scheme II).

Three solutions of (2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine (1*R*)-10-camphorsulfonate (compound of formula **Ib**) in propan-2-ol/water, each prepared from (2*S*,3*S*)-2-benzhydryl-*N*-benzylquinuclidin-3-amine (1*R*)-10-camphorsulfonate (compound of formula **VIa**, 18kg, 29.3 moles) and 5-*tert*-butyl-2-methoxybenzaldehyde (6.47 kg, 33.7 moles) using the Step A (Scheme II) process as previously described, were combined to give a total approximate volume of 430 L of solution. This was then concentrated to a volume of approximately 160 L by distillation under vacuum. Toluene (266kg) was then added and the resultant mixture was concentrated by atmospheric pressure distillation until the volume was approximately 160 L. Water (216 kg) and toluene (250 kg) were then added, and the mixture was then cooled to 20-25°C. The pH of the aqueous phase was adjusted to pH 12.5-12.9 by the addition of aqueous sodium hydroxide with agitation. The aqueous phase was then removed, and the organic phase was concentrated to a volume of approximately 160 L by distillation under vacuum. Water (30.8 kg) and propan-2-ol (218 kg) were then added and the resultant mixture was then concentrated to a volume of approximately 160 L by distillation at atmospheric pressure. At this point, the mixture was held at 25-35°C for 18 hours for convenience. Water (33.8 kg) and propan-2-ol (218 kg) were then added, and the mixture was concentrated to a volume of approximately 160 L by distillation at atmospheric pressure. Water (21 kg) and propan-2-ol (141 kg) were then added, and the mixture was concentrated to a volume of approximately 160 L by distillation at atmospheric pressure. Whilst maintaining the temperature of the reaction mixture above 75°C, propan-2-ol (97 kg) was then slowly added, and the resultant mixture was then cooled to 70°C for 1.5 hours during which time crystallization occurred. The resultant suspension was then cooled to 20-25°C over 5 hours and was stirred at this temperature for 11 hours. The solid was then collected by filtration, and the filter cake was washed twice with propan-2-ol (17 kg and 34 kg). The resultant solid was then dried under vacuum at 50°C to give the title compound (35.3 kg) as a colourless solid. ^{1}H-NMR (300 MHz, $CDCl_3$, 30°C) δ : 7.33 (2H, br d),

7.27-7.10 (8H, m), 7.10-7.01 (1H, m), 6.92 (1H, d), 6.65 (1H, d), 4.51 (1H, d), 3.73-3.52 (5H, m), 3.26-3.09 (2H, m), 2.77 (1H, dd), 2.82-2.73 (2H, m), 2.59 (1H, br t), 2.15-2.06 (1H, m), 2.01-1.87 (1H, m), 1.73-1.60 (1H, m), 1.60-1.43 (1H, m), 1.32-1.19 (10H, m). LRMS (positive atmospheric pressure chemical ionization): m/z [MH^+] 469.

Optional purification of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine, compound of formula I (Step BX, Scheme II).

A suspension of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine (compound of formula **I**, 70 g) in propan-2-ol (350 mL) was heated to reflux for 1 hour to give a solution. The resultant mixture was then cooled to 70-75°C for 2 hours during which time crystallization occurred, and the resultant suspension was then cooled to 20-25 °C over approximately 4 hours. The mixture was then cooled to 0-3°C for 0.5 hours and the solid was then collected by filtration. The filter cake was then washed twice with propan-2-ol (70 mL each) and the resultant solid was dried under vacuum at 50°C to give the title compound (67.7 g) as a colourless solid.

Preparation of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate, compound of formula Ia (Step C, Scheme II).

A solution of (2S,3S)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine (33.95 kg, 72.4 moles) and anhydrous citric acid (15.3 kg, 79.7 moles) in a mixture of acetone (215 kg) and water (13.6 kg) was heated to 38-42°C. The resultant mixture was then transferred to another reactor via an in-line filter. The transfer line and filter were washed through with acetone (54 kg) and these filtered washings were added to the solution. The resultant mixture was then cooled to 20-25°C and filtered *tert*-butyl methyl ether (252kg) was added portion-wise over a period of approximately 35 minutes. The resultant suspension was then granulated at 20-25°C for approximately 20 hours. The solid was then collected by filtration on an agitated filter-dryer and the filter cake was washed twice with filtered *tert*-butyl methyl ether (50kg each). The resultant solid was then dried at 35°C under vacuum with agitation to give the title compound (44.4kg) as a colourless solid. The product was then milled. ^{1}H-NMR (500 MHz, d^4-methanol, 30°C) δ : 7.46 (2H, d), 7.45 (2H, d), 7.37 (4H, m), 7.31 (1H, m), 7.29 (1H, m), 7.24 (1H, dd), 6.95 (1H, d),

6.76 (1H, d), 4.75 (1H, dd), 4.71 (1H, d), 3.76 (1H, m), 3.57 (1H, d), 3.55 (3H, s), 3.37 (1H, m), 3.31 (1H, m), 3.26 (1H, m), 3.24 (1H, d), 3.10 (1H, t), 2.83 (2H, d), 2.75 (2H, d), 2.51 (1H, m), 2.35 (1H, m), 2.11 (1H, m), 2.06 (1H, m), 1.85 (1H, m), 1.29 (9H, s). ^{13}C NMR (125.7 MHz, d^4-methanol, 30°C) δ : 179.4, 175.0, 156.8, 144.0, 141.5, 141.4, 131.1, 130.6, 129.4, 128.9, 128.7, 128.3, 128.2, 127.2, 126.4, 111.0, 74.0, 64.7, 56.1, 54.2, 50.4, 48.5, 48.3, 44.9, 43.8, 34.8, 32.9, 25.3, 22.2, 18.1. LRMS (ES+): m/z [MH$^+$] 469.

The solid Compound of Formula Ia prepared by this process exhibited the following Powder X-Ray Diffaction characteristics:

Table I: Compound of Formula Ia Peak Position Table

°2-Theta	Intensity %	°2-Theta	Intensity %	°2-Theta	Intensity %
6.66	36.80	20.57	20.00	26.34	18.00
8.81	8.40	20.86	37.10	26.62	25.30
11.51	41.90	21.18	12.30	27.36	16.20
11.90	55.40	21.64	20.20	27.97	5.80
13.23	21.70	22.30	12.00	28.47	8.20
13.99	100.00	22.51	28.90	28.81	6.50
14.47	26.40	22.96	18.80	30.57	7.70
15.29	21.40	23.21	22.50	31.00	9.40
15.61	17.60	24.01	5.90	31.42	21.70
16.65	42.40	24.18	8.60	31.79	6.50
17.54	53.90	25.09	15.80	32.33	5.90
17.81	19.80	25.32	9.50	32.74	6.70
18.22	7.00	25.69	5.30	33.32	5.50
19.30	15.50	26.03	11.40	35.19	6.40
20.18	79.90	26.19	14.30		

Powder X-Ray Diffraction pattern acquisition details.

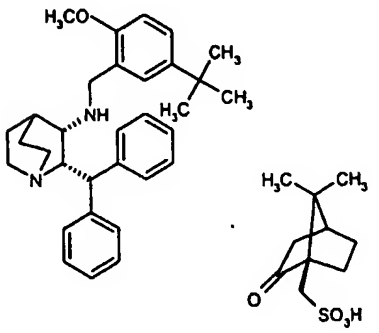
The powder X-ray diffraction pattern was determined using a SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The sample was prepared for analysis by packing the powder into 12mm diameter, 0.25mm deep cavity that had been cut into silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha$_1$ X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40kV/40mA. The analyses were performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 2° to 40°.

Optional purification of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate, compound of formula Ia (Step CX (Scheme II).

A mixture of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine citrate monohydrate (38.47kg, 56.7 moles) and filtered water (11.5 kg) in filtered acetone (213kg) was heated to 38-42°C to achieve a solution, which was then cooled to 33-37°C. To this solution was then added filtered *tert*-butyl methyl ether (201 kg) over a period of approximately 35 minutes whilst maintaining the temperature at 33-37°C. The resultant suspension was then cooled to 20-25°C and was then granulated at this temperature for approximately 19 hours. The solid was then collected by filtration on an agitated filter-dryer and the filter cake was washed twice with filtered *tert*-butyl methyl ether (58 kg each). The resultant solid was then dried at 35°C under vacuum with agitation to give the title compound (32.9 kg) as a colourless solid. The product was then milled.

Preferred Embodiments

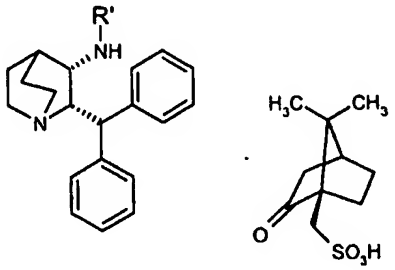
1. A process for preparing the compound of Formula **Ib**,



Ib

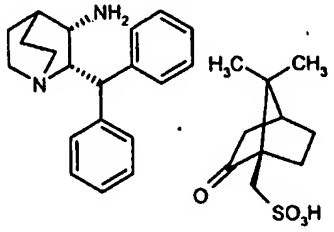
comprising:

(a) deprotecting a compound of Formula **VIa**,



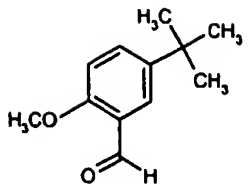
VIa

wherein R' is a protecting group, to provide a compound of Formula **VII**;



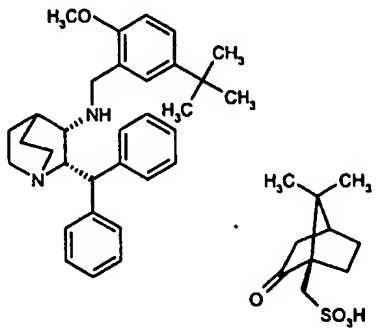
VII

(b) reacting the compound of formula **VII** so formed with a compound of formula **VIII**,



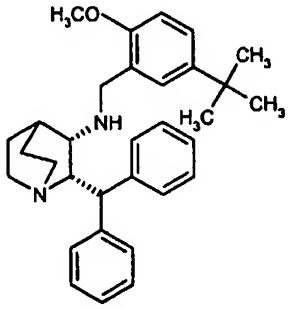
VIII

and performing a reductive amination to provide a compound of Formula **Ib**,



Ib

2. The process according to Preferred embodiment 1 further comprising removing the camphorsulfonate salt of the compound of Formula **Ib** to provide a compound of Formula **I**,



I

3. The process according to Preferred embodiment 2, wherein the protecting group is benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, or triphenylmethyl.

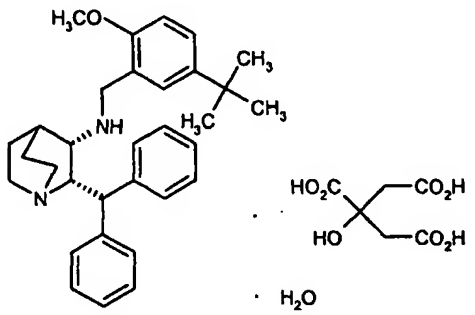
4. The process according to Preferred embodiment 3, wherein the deprotection is performed by catalytic hydrogenolysis with hydrogen.

5. The process according to Preferred embodiment 4, wherein the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

6. The process according to Preferred embodiment 5, wherein the reductive animation is performed by formation of an imine followed by catalytic hydrogenation.

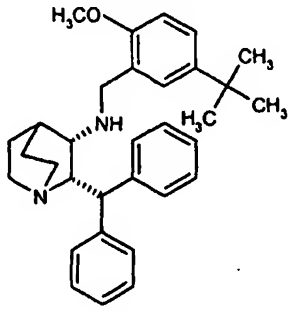
7. The process according to Preferred embodiment 6, wherein the hydrogenation catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

8. The process according to Preferred embodiment 7 further comprising treating the compound of Formula I with citric acid, forming the compound of Formula **Ia**.



Ia – citrate monohydrate

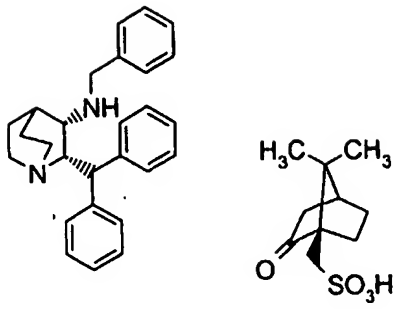
9. A process for preparing the compound of Formula **I**,



I

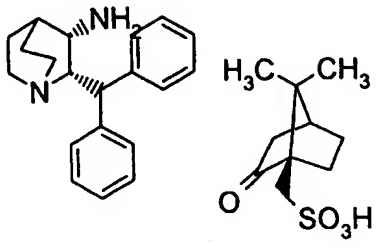
comprising:

(a) debenzylating a compound of Formula **VIa**



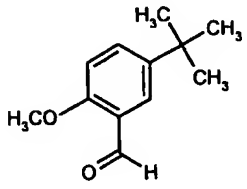
VIa

to provide a compound of Formula **VII**;



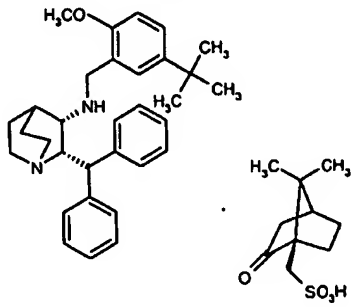
VII

(b) reacting the compound of formula **VII** so formed with a compound of formula **VIII**,



VIII

and performing a reductive amination to provide a compound of Formula **Ib**,



Ib , and

(c) removing the camphorsulfonate salt of the compound of **Ib** to provide the compound of Formula **I**.

10. The process according to Preferred embodiment 9 wherein the debenzylation is performed by catalytic hydrogenation.

11. The process according to Preferred embodiment 10 wherein the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

12. The process according to Preferred embodiments 9, 10 or 11 further comprising a reductive amination of step (b) that is performed by catalytic hydrogenation.

13. The process according to Preferred embodiment 12, wherein the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

14. The process according to Preferred embodiment 13 further comprising isolating the compound of Formula **I**.

15. The process according to Preferred embodiment 14 wherein the isolation of the compound of Formula **I** occurs by acid counter ion exchange or basification followed by selective crystallization.

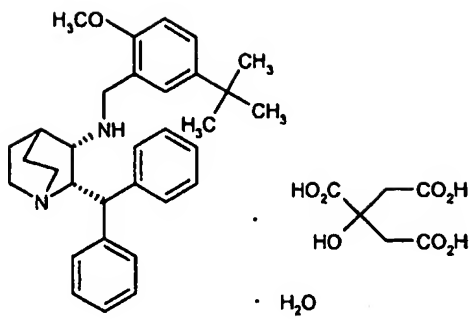
16. The process according to Preferred embodiment 15 wherein the crystallization is accomplished in a solvent selected from water, alcohols, ethers, hydrocarbons or mixtures thereof.

17. The process according to Preferred embodiment 16 wherein the solvent is isopropanol, toluene or water or mixtures thereof.

18. The process according to Preferred embodiment 15 wherein the basification is performed by the addition of an inorganic or organic reagent.

19. The process according to Preferred embodiment 18 wherein the reagent is sodium hydroxide, sodium carbonate or sodium bicarbonate.

20. The process according to Preferred embodiment 9 further comprising treating the compound of Formula I with citric acid, forming the compound of Formula **Ia**



Ia -- citrate monohydrate

21. The process according to Preferred embodiment 20 further comprising the addition of acetone and water.

22. The process according to Preferred embodiment 21 further comprising

(a) filtering the solution; and

(b) adding a filtered ether solvent,

providing a compound of Formula **Ia**.

23. The process according to Preferred embodiment 22 further comprising the additional step (c) of granulating the compound of Formula **Ia**.

24. The process according to Preferred embodiment 22 wherein the ether solvent is tert-butyl methyl ether.

25. The process according to Preferred embodiment 22 further comprising applying heat at an elevated temperature during step (b).

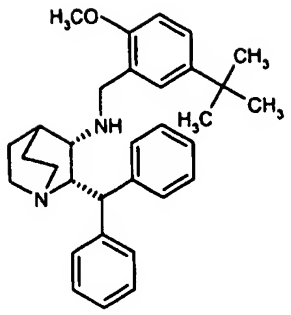
26. The process according to Preferred embodiment 22 further comprising the addition of seed crystals of Compound of Formula **Ia** during or after step (b).

27. The process according to Preferred embodiment 25 wherein the temperature is about 30°C to about 45°C.

28. The process according to Preferred embodiment 23 further comprising granulating the compound of Formula **I** at an elevated temperature.

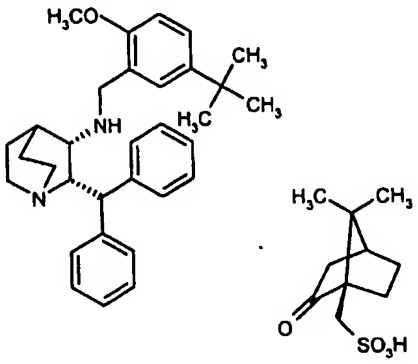
29. The process according to Preferred embodiment 28 wherein the temperature is about 30°C to about 45°C.

30. A process for preparing the compound of Formula **I**,



I

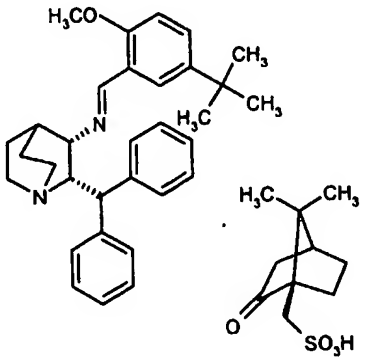
comprising removing the camphorsulfonate salt of a compound of **Ib**,



Ib

to provide the compound of Formula **I**.

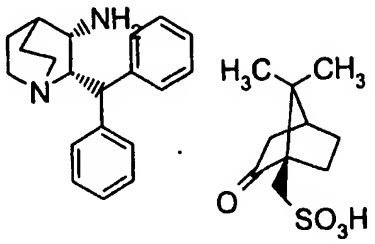
31. The process according to Preferred embodiment 30 further comprising reducing a compound of **IXa**,



IXa

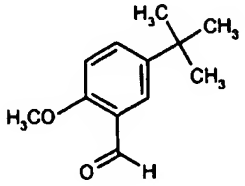
to provide the compound of Formula **Ib** so formed.

32. The process according to Preferred embodiment 31 further comprising reacting a compound of Formula **VII**,



VII

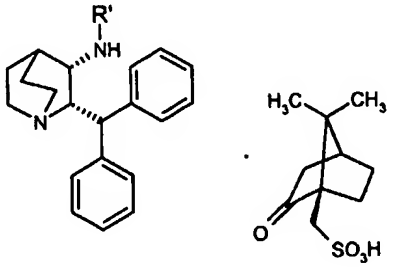
with a compound of Formula **VIII**,



VIII

to provide the compound of formula **IXa** so formed.

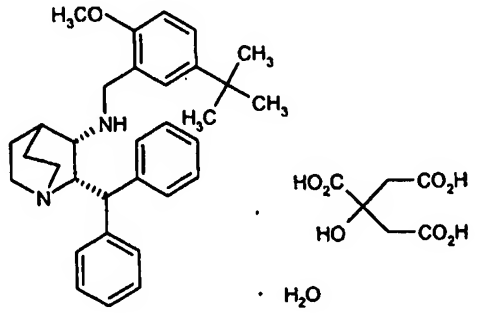
33. The process according to Preferred embodiment 32 further comprising deprotecting a compound of Formula **VIa**,



VIa

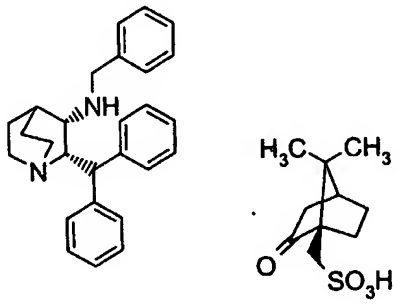
wherein R' is a protecting group selected from benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl or triphenylmethyl, to provide the compound of Formula **VII** so formed.

34. The process according to Preferred embodiments 30, 31, 32 and 33 further comprising treating the compound of Formula I with citric acid to form a compound of Formula **Ia**,



Ia – citrate monohydrate

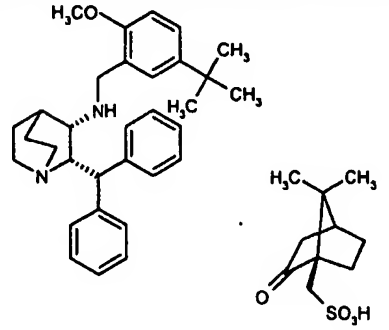
35. A compound of the Formula VIa



VIa

CLAIMS

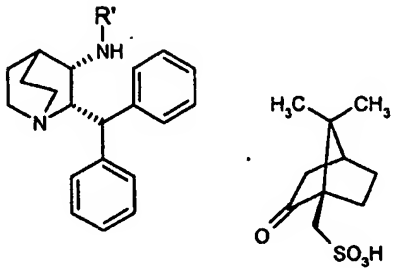
1. A process for preparing the compound of Formula **Ib**,



Ib

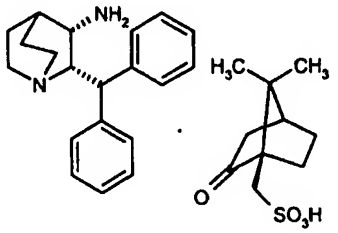
comprising:

(c) deprotecting a compound of Formula **VIa**,



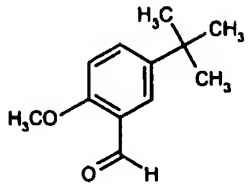
VIa

wherein R' is a protecting group, to provide a compound of Formula **VII**;



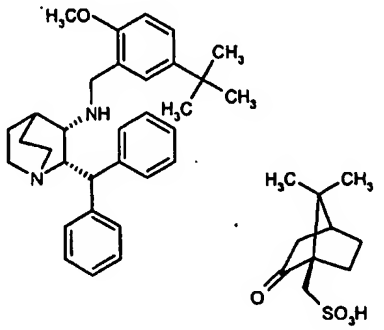
VII

(d) reacting the compound of formula VII so formed with a compound of formula VIII,



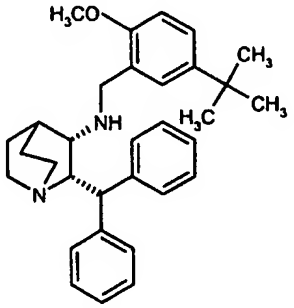
VIII

and performing a reductive amination to provide a compound of Formula Ib,



Ib

2. The process according to Claim 1 further comprising removing the camphorsulfonate salt of the compound of Formula Ib to provide a compound of Formula I,



I

3. The process according to Claim 1 or Claim 2, wherein the protecting group is benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, or triphenylmethyl.

4. The process according to Claim 3, wherein the deprotection is performed by catalytic hydrogenolysis with hydrogen.

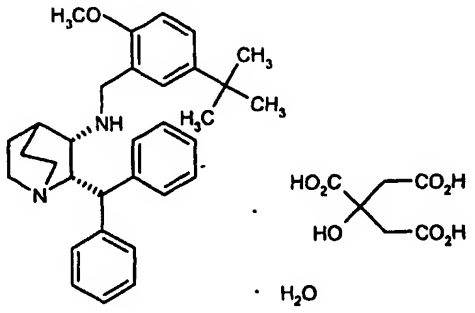
5. The process according to Claim 4, wherein the catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

6. The process according to any preceding Claim wherein the reductive animation is performed by formation of an imine followed by catalytic hydrogenation.

7. The process according to Claim 6, wherein the hydrogenation catalyst is palladium on carbon, platinum on carbon, palladium on calcium carbonate, or palladium on alumina (Al_2O_3).

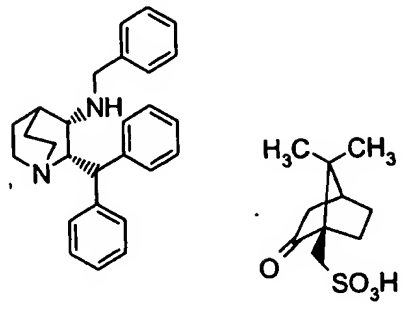
8. The process according to any of Claims 2 to 7 further comprising isolating the compound of Formula I.

9. The process according to any of Claims 2 to 8 further comprising treating the compound of Formula I with citric acid, forming the compound of Formula Ia



Ia – citrate monohydrate

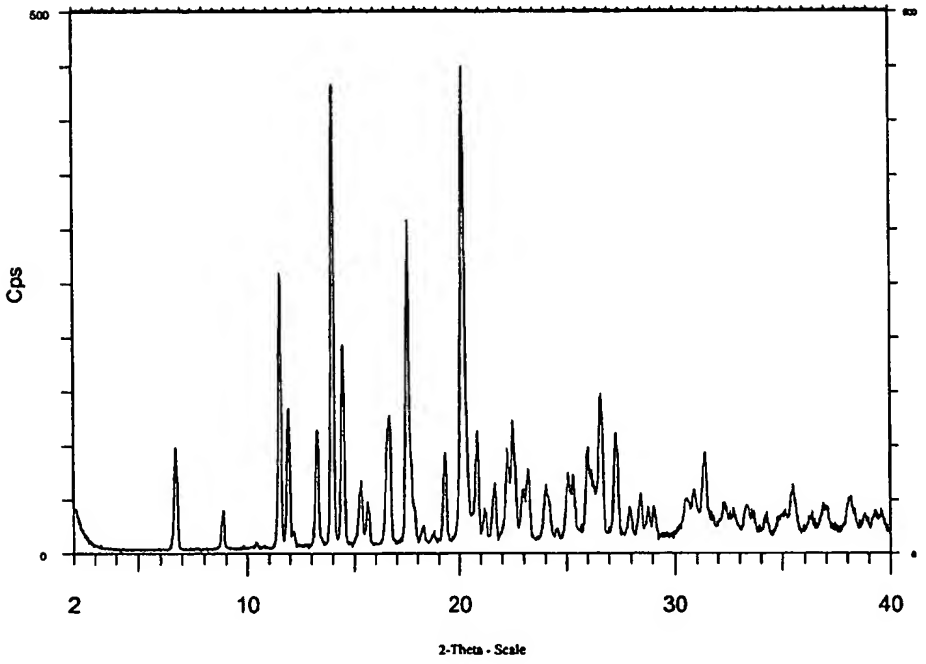
10. A compound of the Formula VIa,



VIa

5

Figure 1: Compound of Formula Ia PXRD Pattern



INTERNATIONAL SEARCH REPORT

Internl Application No
PCT/IB2005/000221

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D453/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/03984 A (PFIZER INC; TICKNER, DEREK, L; MELTZ, MORGAN) 6 February 1997 (1997-02-06) page 8, line 5; claims 1,6 page 8 - page 9	1-10
A	US 6 222 038 B1 (ITO FUMITAKA ET AL) 24 April 2001 (2001-04-24) cited in the application column 5, line 6 - column 6, line 64; example 1 column 7, last paragraph	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2005	17/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WARAWA E J ET AL: "Quinuclidine chemistry. 4. Diuretic properties of cis-3-amino-2-benzhydrylquinuclidine." JOURNAL OF MEDICINAL CHEMISTRY. JUN 1975, vol. 18, no. 6, June 1975 (1975-06), pages 587-593, XP002327149 ISSN: 0022-2623 Scheme 1 page 587	1-10
A	US 6 255 320 B1 (QUALLICH GEORGE JOSEPH ET AL) 3 July 2001 (2001-07-03) cited in the application claims 1,8	9
P,A	WO 2004/035575 A (PFIZER PRODOUCTS, INC; DSM PHARMACEUTICALS, INC; NUGENT, THOMAS, C; SE) 29 April 2004 (2004-04-29) cited in the application page 3, last paragraph; examples page 3, line 1 - line 4	1-10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000221

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703984 A	06-02-1997	AT 250600 T	15-10-2003
		AU 697553 B2	08-10-1998
		AU 6134896 A	18-02-1997
		CA 2227194 A1	06-02-1997
		CN 1190970 A ,C	19-08-1998
		CZ 9800150 A3	17-02-1999
		DE 69630123 D1	30-10-2003
		DE 69630123 T2	08-04-2004
		DK 840735 T3	09-02-2004
		EP 0840735 A1	13-05-1998
		ES 2205039 T3	01-05-2004
		HK 1010195 A1	16-11-2001
		HU 9900238 A2	28-05-1999
		WO 9703984 A1	06-02-1997
		JP 3043074 B2	22-05-2000
		JP 10511102 T	27-10-1998
		NO 980211 A	16-03-1998
		NZ 310539 A	25-11-1998
		PL 324610 A1	08-06-1998
		PT 840735 T	27-02-2004
		RU 2136681 C1	10-09-1999
		US 6008357 A	28-12-1999
		ZA 9606026 A	16-01-1998
US 6222038 B1	24-04-2001	AP 299 A	14-01-1994
		AT 135006 T	15-03-1996
		AU 657552 B2	16-03-1995
		AU 1990192 A	08-01-1993
		BG 61694 B1	31-03-1998
		BG 98248 A	15-07-1994
		BR 9206073 A	06-12-1994
		CA 2102179 A1	01-12-1992
		CN 1067428 A ,C	30-12-1992
		CZ 9203906 A3	16-02-1994
		DE 9290063 U1	24-02-1994
		DE 69208877 D1	11-04-1996
		DE 69208877 T2	25-07-1996
		DK 587723 T3	01-04-1996
		EG 19944 A	27-02-1997
		EP 0587723 A1	23-03-1994
		ES 2084361 T3	01-05-1996
		FI 935297 A	29-11-1993
		GR 3019687 T3	31-07-1996
		HU 70151 A2	28-09-1995
		IE 921729 A1	02-12-1992
		IL 102008 A	08-12-1995
		JP 2645225 B2	25-08-1997
		JP 7285965 A	31-10-1995
		JP 7033386 B	12-04-1995
		JP 6504292 T	19-05-1994
		KR 214905 B1	02-08-1999
		MA 22539 A1	31-12-1992
		MX 9202554 A1	01-11-1992
		NO 934312 A	29-11-1993
		NZ 242956 A	27-06-1995
		NZ 270673 A	27-07-1997
		OA 9867 A	15-08-1994
		PL 171379 B1	30-04-1997

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6222038 B1		PT 100546 A ,B	31-08-1993
		RO 110499 B1	30-01-1996
		RU 2103269 C1	27-01-1998
		SK 390692 A3	04-02-1998
		WO 9221677 A1	10-12-1992
		US 5807867 A	15-09-1998
		US 5939433 A	17-08-1999
		ZA 9203942 A	29-11-1993
US 6255320 B1	03-07-2001	AT 244239 T	15-07-2003
		AU 767334 B2	06-11-2003
		AU 4424800 A	18-12-2000
		BG 106204 A	31-07-2002
		BR 0011094 A	19-03-2002
		CA 2372238 A1	07-12-2000
		CN 1353711 A ,C	12-06-2002
		CZ 20014269 A3	17-04-2002
		DE 60003679 D1	07-08-2003
		DE 60003679 T2	27-05-2004
		DK 1181290 T3	29-09-2003
		EA 3731 B1	28-08-2003
		EE 200100656 A	17-02-2003
		EP 1181290 A1	27-02-2002
		ES 2199825 T3	01-03-2004
		HK 1046284 A1	08-02-2005
		HR 20010904 A1	28-02-2003
		HU 0201301 A2	28-08-2002
		WO 0073304 A1	07-12-2000
		JP 2003501354 T	14-01-2003
		MX PA01012325 A	22-07-2002
		NO 20015848 A	18-12-2001
		NZ 515349 A	26-03-2004
		PL 352716 A1	08-09-2003
		PT 1181290 T	30-09-2003
		SI 1181290 T1	31-12-2003
		SK 17332001 A3	02-07-2002
		TR 200103473 T2	22-04-2002
		ZA 200109775 A	28-11-2002
WO 2004035575 A	29-04-2004	AU 2003277353 A1	04-05-2004
		WO 2004035575 A1	29-04-2004
		US 2004116704 A1	17-06-2004